



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Li et al.

Serial No.: 09/817,538

Examiner: K. Lacourciere

Filed: August 6, 2001

Group Art Unit: 1635

Entitled: ANTISENSE OLIGONUCLEOTIDE INHIBITION OF  
SPECIFIC HISTONE DEACETYLASE ISOFORMS

Attorney

Docket No.: MET-021US2

Assistant Commissioner for Patents  
Washington, D.C. 20231

APPEAL BRIEF

Hon. Assistant Commissioner for Patents:

Applicant hereby appeals from the final rejection of Claims 1-3 and 5 of the above identified patent application.

I. Real Party of Interest

The present application is wholly owned by MethylGene, Inc., by assignment by the inventors as recorded at Reel/Frame 012081/0968.

II. Related Appeals and Interferences

There are no current appeals or interferences which would directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1-36 were originally filed in the instant application. Claims 4, 6 and 8-36 were canceled during prosecution without prejudice. Claims 1-3 and 5 are currently pending in this Appeal.

IV. Status of Amendments

Claim 7 was amended subsequent to the Final rejection to correct the recitation of the claim to which Claim 7 depends upon. This amendment was entered by the Examiner in the Advisory Action mailed from the U.S. Patent and Trademark Office (USPTO) on September 25, 2003. Appellants also acknowledge that in the Office Action mailed from the USPTO on May 6, 2003, the Examiner found Claim 7, as amended, to be free of prior art.

V. Summary of Invention

The invention relates to the inhibition of histone deacetylase expression. Specifically, the invention provides oligonucleotides that inhibit one or more histone deacetylase isoforms, but less than all histone deacetylase isoforms, by inhibiting expression at the nucleic acid level (See Detailed Description at page 15, line 14 to page 16, line 4). The claimed oligonucleotide can be a chimeric or hybrid oligonucleotide and have a variety of modifications (See Detailed Description at page 18, line 5 to page 20, line 9).

VI. Issues

The sole issue to be determined in this Appeal is whether Claims 1-3 and 5 are unpatentable over Yoshida et al. in view of the collection of Taylor *et al.*, (DDT vol. 4, No. 12, 12/12/99, pages 562-567), Bennett *et al.*, (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Baracchini *et al.*, (U.S. Patent 5,801,154), Cowser (U.S. Patent 5,951,455) and the sequence of HDAC-1 (GenBank Accession No. U50079).

VII. Argument

Claims 1-3 and 5 are rejected as being unpatentable over Yoshida *et al.*, (hereinafter "Yoshida"), in view of the collection of Taylor *et al.*, (DDT vol. 4, No. 12, 12/12/99, pages 562-567), Bennett *et al.*, (Chapter 2, pages 13-46, from Methods in Molecular Medicine:

Antisense Therapeutics, 1996), Baracchini *et al.*, (U.S. Patent 5,801,154), Cowser (U.S. Patent 5,951,455) and the sequence of HDAC-1 (GenBank Accession No. U50079).

As previously argued, the combination of Yoshida and others fails to render the claimed invention obvious because there is no motivation or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. According to the Examiner, the motivation to combine Yoshida with the other references is that Yoshida taught the need for “the use of a **more specific and potent inhibitor** of histone deacetylase... to carry out further more refined analysis” (emphasis added). However, the Examiner continues to take this statement out of context.

Yoshida describes that prior to their publication n-butyrate, a small molecule inhibitor of histone deacetylase, was used with pleiotropic effects on other enzymes, cytoskeleton, cell membranes, etc. Thus, the technical problem faced by Yoshida was to find a more specific and potent inhibitor of histone deacetylase than n-butyrate. Yoshida solved this problem by using another small molecule inhibitor of histone deacetylase referred to as (R)-Trichostatin A (hereinafter “TSA”).

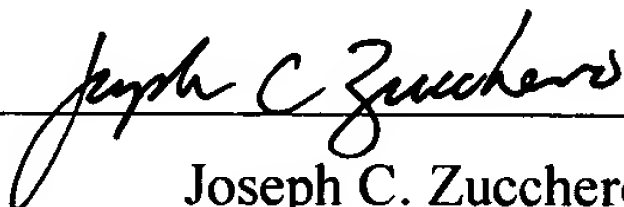
Yoshida describes a technical problem and its solution. Yet the Examiner maintains that Yoshida not only provides the motivation to find further “more specific and potent inhibitors” of histone deacetylase but also provides the motivation to look outside the small molecule inhibitor art to antisense technology even though (a) TSA is the more specific and potent inhibitor Yoshida describes a need for and (b) there is no mention, explicitly or implicitly, within Yoshida that antisense technology could be used to provide specific and potent inhibitors of histone deacetylase. The level of skill in the art cannot be relied upon to provide the suggestion to combine references (See *Al-Site Corp. v. VSI Int’l Inc.*, 174 F.3d 1308, (Fed. Cir. 1999)). Therefore, Yoshida, at best, provides the motivation to find a better “small molecule” inhibitor of histone deacetylase or to optimize TSA. However, it would still be a stretch to find the motivation to do this, either explicitly or implicitly, within Yoshida.

An Examiner is not free to pick and choose references in an attempt to provide the teaching or suggestion of all the claimed limitations of the instant invention. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Yoshida describes the problem of using the small molecule inhibitor n-butyrate and teaches the solution to the problem through the use of another small molecule inhibitor, TSA. Yoshida provides no motivation or suggestion regarding the desirability to look for further inhibitors of histone deacetylase, much less to look for such inhibitors in the alternative art of antisense technology. The need to combine five references to maintain this rejection further emphasizes this point.

Accordingly, Appellants respectfully reiterate that there is no motivation in the prior art to combine the cited references. Thus, Appellants respectfully request that the rejection of Claims 1-3 and 5 for obviousness be withdrawn.

Respectfully submitted,

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## Appendix

### MET-021US2 – Claims as pending on Appeal

1. (Previously Amended) An oligonucleotide having nucleotide sequence of from 15 to about 26 nucleotides that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA that encodes a portion of HDAC-1 (SEQ ID NO: 2).
2. (Original) The oligonucleotide according to claim 1, wherein the oligonucleotide is a chimeric oligonucleotide.
3. (Original) The oligonucleotide according to claim 1, wherein the oligonucleotide is a hybrid oligonucleotide.
4. CANCELLED.
5. (Original) The oligonucleotide according to claim 1 having one or more phosphorothioate internucleoside linkage, being 20-26 nucleotides in length, and being modified such that the terminal four nucleotides at the 5' end of the oligonucleotide and the terminal four nucleotides at the 3' end of the oligonucleotide each have 2'-O-methyl groups attached to their sugar residues.
6. CANCELLED.
7. (Previously Amended) The oligonucleotide according to claim 1 ~~6~~ that is SEQ ID NO: 17 or SEQ ID NO: 18.
- 8-36 CANCELLED.